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STABILITY INDICATING METHODS AND FORCED DEGRADATION STUDIES FOR PHARMACEUTICAL PRODUCTS SAFETY AND EFFICACY- AN OVERVIEW

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ABSTRACT

Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidances state the requirement of stability testing data to understand how the quality of a drug substance and drug product changes with time under the influence of various environmental factors. Stability testing of drugs requires an accurate analytical method that quantifies active pharmaceutical ingredients (API) without interference from degradation products, process impurities and other potential impurities. Stability-indicating methods are traditionally performed using gradient elution, in order to ensure that degradants of various chemical compositions are all detected. Relevant stress conditions are light, heat, humidity, hydrolysis (acid / base influence) and oxidation or even a combination of described parameters. Stability-indicating HPLC methods are designed for drugs. Stability-indicating analytical method is validated, specific, and quantitative analytical method, which is capable of accurately testing API, degradation products, and other components of interest without interference. The stability-indicating method is used to detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product. The forced degradation studies are another very important part of the validation of the stability indicating method.

KEYWORD: Chemical stability, Stability testing, Degradation products, Forced degradation studies, Stability-indicating methods, Active pharmaceutical ingredients.

INTRODUCTION

Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidances state the requirement of stability testing data to understand how the quality of a drug substance and drug product changes with time under the influence of various environmental factors. Knowledge of the stability of molecule helps in selecting proper formulation and package as well as providing proper storage conditions and shelf life, which is essential for regulatory documentation. Stability testing of drugs requires an accurate analytical method that quantifies active pharmaceutical ingredients (API) without interference from degradation products, process impurities and other potential impurities.[1] Stability-indicating HPLC methods are designed for drugs. Stability-indicating analytical method is validated, specific, and quantitative analytical method, which is capable of accurately testing API, degradation products, and other components of interest without interference.[2]

The stability-indicating method is used to detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product. The quality of a drug product depends on the quality of API.[1] The changes in API itself and related impurities have to be examined throughout the drug life. An ideal situation is that the API and all the impurities can be accurately measured with one method. Nevertheless, secondary validated complemented method may also be used when a single method is unattainable to examine all of the components at the same time. Stability information is needed for regulatory submissions such as IND (Investigational New Drug Application) and NDA (New Drug Applications) and to set expiration dates for the API or drug product.

The forced degradation studies are another very important part of the validation of the stability indicating method. In forced degradation studies, samples are stored under extreme conditions (acid, base, peroxide, heat, light, humidity etc) in order to rapidly screen drug product stabilities. Stability-indicating methods are traditionally performed using gradient elution, in order to ensure that degradants of various chemical compositions are all detected.[1] Relevant stress conditions are light, heat, humidity, hydrolysis (acid / base influence) and

oxidation or even a combination of described parameters. If it is necessary to form degradation products, the strength of stress conditions can vary due to the chemical structure of the drug substance, the kind of drug product, and product specific storage requirements. A typical study design should be able to cover different stress conditions using different time periods in order to assess the degradation kinetics.

STABILITY INDICATING METHOD

A stability indicating method (SIM) is an analytical procedure used to quantitate the decrease in the amount of the active pharmaceutical ingredient (API) in drug product due to degradation. According to an FDA guidance document, a stability-indicating method is a validated quantitative analytical procedure that can be used to detect how the stability of the drug substances and drug products changes with time. A stability-indicating method accurately measures the changes in active ingredients concentration without interference from other degradation products, impurities and excipients.[1] Stress testing is carried out to demonstrate specificity of the developed method to measure the changes in concentration of drug substance when little information is available about potential degradation product. The development of a suitable stability-indicating method provides a background for the pre-formulation studies, stability studies and the development of proper storage requirements. The HPLC is a most widely used analytical tool for separation and quantifying the impurities and it is most frequently coupled with a UV detector.[2]

Importance of development of stability-indicating analytical methods

A stability indicating method (SIM) is an analytical procedure used to quantitate the decrease in the amount of the active pharmaceutical ingredient (API) in drug product due to degradation. According to an FDA guidance document, a stability-indicating method is a validated quantitative analytical procedure that can be used to detect how the stability of the drug substances and drug products changes with time. A stability-indicating method accurately measures the changes in active ingredients concentration without interference from other degradation products, impurities and excipients.[1] Stress testing is carried out to demonstrate specificity of the developed method to measure the changes in concentration of drug substance when little information is available about potential degradation product. The development of a suitable stability indicating method provides a background for the pre-formulation studies, stability studies and the development of proper storage requirements.

Stress testing route to the development of stability-indicating analytical methods (SIAMs)

Forced degradation is a technique where different stress conditions are applied over drug substances and which in turn different degradation products are produced.[3] These studies are also called as stress testing or stress degradation studies. These methods are mainly used for the determination of stability of molecule under accelerated conditions.[4] It is known that regulatory documentation process, selection of proper storage and package conditions, and selection of formulation are dependent on the stability of molecules.[5] In forced degradation process, general conditions such as light, heat, humidity, and oxidation are accelerated individually or in combination with automated stress to accelerate the degradation of the molecule by physical or chemical means.[6,7] As per the International Committee for Harmonization (ICH) guidelines, the stability of the molecule, different degradative pathways, and validation of the developed stability procedures are studied using forced decomposition studies. The details of drug molecules that undergoes degradation and the different products that are formed with respect to time changes under the impact of different environmental parameters and understanding of stability data are well explained using the Food and Drug Administration (FDA) and ICH guidelines.[8,9]

Forced degradation studies act as a tool for the estimation of stability of the drug. Stability of the drug, which in turn affects the drug purity, potency, and safety can be determined by these forced degradation studies. Therefore, stability is considered as a critical parameter. Any alteration in stability can cause lowering of dose and thus make the dosage forms to be toxic.[3]

Degradation studies are important to determine the inference of degradation routes and stability of pharmaceuticals under various stress conditions. Characterization of the degradants produced is usually carried out according to ICH guidelines.

Different analytical equipment are employed to determine the stability studies. For instance, high-performance liquid chromatography-ultraviolet (HPLC-UV) and HPLC-photodiode array detector (PDA) are two common equipment to study the stability indicating method (SIM) development and validation purpose, while LC coupled to mass spectrometry (LC-MS) has become the authentic technique for characterization of degradant products (DP). LC-MS has gained enormous importance due to its high DP sensitivity and selectivity and in addition also provides a detailed structural information about the different DP.[10]

Degradation Limit

The regulatory agencies have defined the limits of degradation products in their guidelines. It is mentioned that 5–20% degradation is accepted for validation of chromatographic assays. In case of small molecules, stability limit should be more than 90% and hence about 10% degradation is sufficient. In general, for monitoring drug product stability, spiked samples of mixture of known degradation products and drug substances are used, which ease out the process of determining the

products that are observed during the degradation. If the drug sample displays any change in the physical and chemical nature, change in activity during the shelf life, then the drug molecule is considered to have undergone degradation. If no such degradation was observed, then either the study will be aborted or the respective drug sample will be subjected to additional stress to analyze the nature of secondary degradants that are expected to produce during the study. If any case only a little or no degradants are produced due to additional stress, then the drug substance will be exposed to excess energy to estimate the stability of molecules.[4, 6]

Origin of Degradation Products

Degradation is considered as one of the chief sources for impurities. Under different stress conditions, namely humidity, heat, pH, isolation, storage, and transportation processes, drug molecules may undergo degradation because of chemical instability. Forced degradation can be carried out through various pathways including hydrolysis, oxidation, heat, and photolysis. It is also observed from different studies that under different stress conditions it is possible to produce all possible types of degradants.[11,12]

Selection of Degradation Conditions[3-5,7,10,11,13-18]

Earlier, intrinsic stability of drugs can be determined using normal conditions such as high temperature and pH. Later, the drug molecules were subjected to additional stress to study the stability. To study the degradation, the solution containing the drug sample was refluxed for a definite time. During this time, if any degradation products were observed, the process would be stopped; further isolation, identification, and characterization of the observed degradation products will be carried out. If no degradation was observed, the reaction time would be increased to observe any signs of degradation due to the extension of time. The frequently used forced degradation conditions are presented in Table 1 and Figure 1.

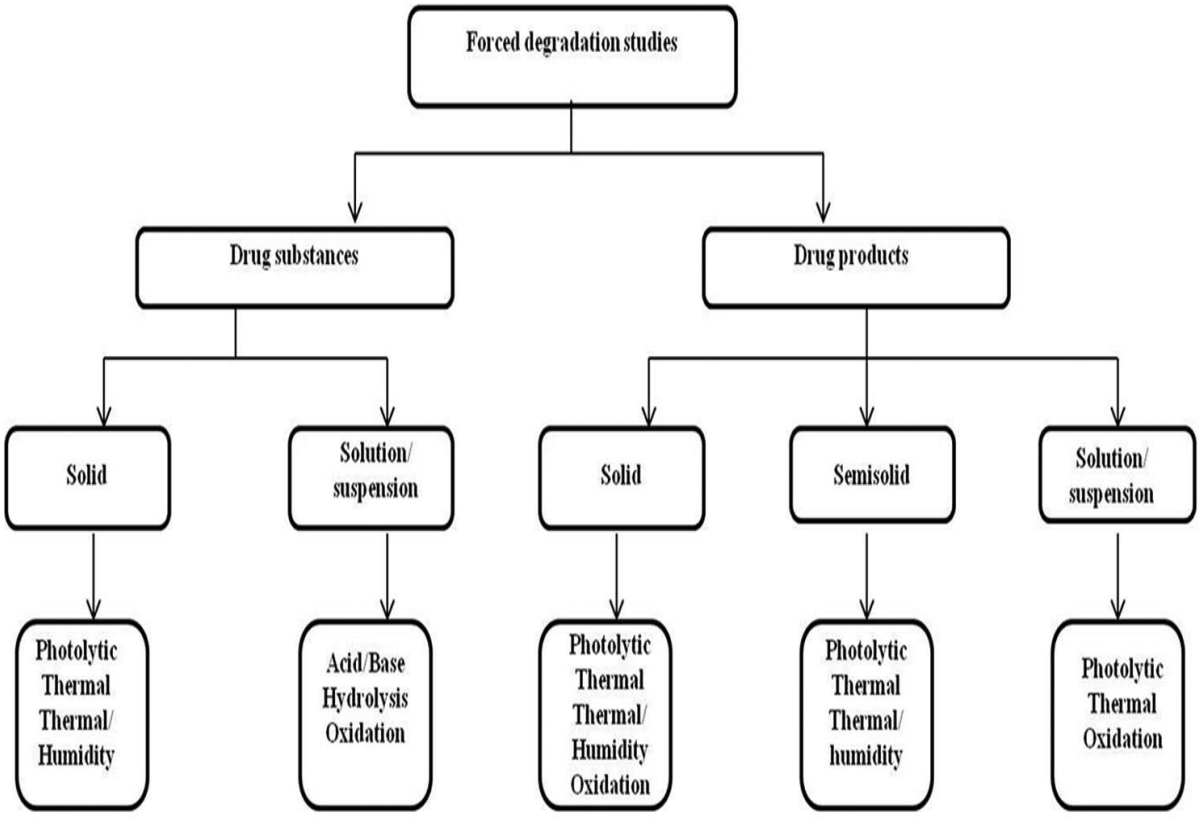

Table 1: Frequently used conditions for forced degradation studies.

Type of degradation	Experimental conditions	Storage conditions	Sampling time (days)
Hydrolysis	Control API (no acid/base)	40°C, 60°C	1,3,5
	0.1M HCl	40°C, 60°C	1,3,5
	0.1M NaOH	40°C, 60°C	1,3,5
	Acid control (no API)	40°C, 60°C	1,3,5
	Base control (no API)	40°C, 60°C	1,3,5
	pH: 2,4,6,8	40°C, 60°C	1,3,5
Oxidation	3% H2O2	25°C, 60°C	1,3,5
	Peroxide control	25°C, 60°C	1,3,5
	Azobisisobutyronitrile (ABIN)	25°C, 60°C	1,3,5
	ABIN control	25°C, 60°C	1,3,5
Photolysis	Light 1 X ICH	NA	1,3,5
	Light 3 X ICH	NA	1,3,5
	Light 3 X ICH	NA	1,3,5
Thermolysis	Heat chamber	60°C	1,3,5
	Heat chamber	60°C/75°C% RH	1,3,5
	Heat chamber	60°C	1,3,5
	Heat chamber	60°C/75°C% RH	1,3,5

RELATION BETWEEN FORCED DEGRADATION STUDIES AND STABILITY DATA

In forced degradation studies, several products are produced than normal stability testing. In stability testing, it becomes difficult to detect the actual degradation products because of its low potential. In this perspective, forced degradation studies minimize this problem. If no degradants was produced, then it can be considered that the drug substance is stable under given stress conditions and the protocol can be depicted to be a stability indicating process. Forced degradation analysis also helps to study the proper storage conditions of different pharmaceuticals. More importantly, forced degradation studies are useful in determining the degradation pathway of various drug substances.[19]

PREPARATION OF SAMPLE FOR FORCED DECOMPOSITION STUDIES

During forced decomposition and stability studies, active pharmaceutical ingredient is subjected to various stress under accelerated conditions such as photolytic, thermal, oxidative, and hydrolytic conditions. Due to stress conditions, several degradation products are expected to be produced, which can be compared to the degradative products (if any) that are obtained from regular storage conditions.[5]

Hydrolytic Conditions

Drugs molecules are dissolved in hydrochloric acid or sulfuric acid (0.1–1 M) in acid hydrolysis. In base hydrolysis drug molecules are dissolved in 0.1–1 M of potassium hydroxide or sodium hydroxide. Samples are subjected to stress for 2–7 days at room temperature. Stressed samples were neutralized with relevant acids or bases to prevent additional degradation.

Oxidation Conditions

Drug molecules are stressed with 0.1–3% hydrogen peroxide. Samples are stressed for not more than 7 days at room temperature and samples are neutralized with suitable agents.

Photolytic Conditions

Sample solutions that are subjected to photolytic stress by exposing them to as minimal as of 1.2 million × l h and 200 W h/m2 light of 300–800 nm.

Thermal Conditions

Solids are exposed to wet heat and liquids are exposed to dry heat. Thermal stress conditions are applied for shorter period.

METHOD DEVELOPMENT AND OPTIMIZATION

Before developing a method, the first step is to determine the pKa value, log P, solubility, and λmax of the respective drug. Development of a reverse phase method using HPLC is a common practice for the separation drugs. The commonly used solvents such as methanol, acetonitrile, and water are used as mobile phases in different combinations and proportions. With respect to the solubility profile of the drug, the organic phase such as methanol or acetonitrile is chosen. The choice of the mobile phase and its proportion is usually determined from earlier reports or by trial and error methods. At the onset of the experiment, the organic and aqueous phases are maintained at 50:50, and further optimization can be done on the proportions of the solvents for the mobile phase such that an ideal resolution of the peaks are obtained. In certain cases, buffers can be used for good baseline separation and peak symmetry. At times, the column temperature is adjusted to 30–40°C to get good reproducibility of the results. Degradant peaks are pushed in the chromatogram to get good resolution. Sometimes degradants peaks elute along with the drug peak or hidden by drug peaks, which in turn leads to peak purity analysis. Direct analysis can be done using HPLC that are equipped with PDA detectors. By changing the proportion of the mobile phase, it becomes

easier to resolve and analyze the degradants peaks. The method developed is considered as homogeneous if the degradants peak is observed where the area under the curve of drug peak and its percentage are not affected. These degradants, which coelute with drug, are acceptable to some extent provided; they were not observed in accelerated and long-term storage studies. Further, the method can be optimized by modifying the parameters such as the rate of flow of mobile phase, volume of sample injected, type of column used, and by changing the proportion of the mobile phase used in the analysis. After optimization of these parameters, the method developed for the study will be subjected to validation as per the ICH guidelines.[5]

Method Validation

The developed SIM is then validated according to USP/ICH guideline for linearity, accuracy, precision, specificity, quantitation limit, detection limit, ruggedness and robustness of the method. It is required to isolate, identify and quantitate the degradants found to be above identification threshold (usually 0.1%).[20,21] If the method does not fall within the acceptance criteria for validation, the method is modified and revalidated.[22]

CONCLUSION

Stability-indicating method is a validated quantitative analytical procedure that can be used to detect how the stability of the drug substances and drug products changes with time. A stability-indicating method accurately measures the changes in active ingredients concentration without interference from other degradation products, impurities and excipients. Forced degradation studies act as a tool for the estimation of stability of the drug. Stability of the drug, which in turn affects the drug purity, potency, and safety can be determined by these forced degradation studies.

Different analytical equipment are employed to determine the stability studies. For instance, high-performance liquid chromatography-ultraviolet (HPLC-UV) and HPLC-photodiode array detector (PDA) are two common equipment to study the stability indicating method (SIM) development and validation purpose.

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